

## CYP2D6: citalopram/escitalopram 1998/1999/2000

95% CI = 95% confidence interval, AUC = area under the concentration-time curve,  $Cl_{or}$  = oral clearance,  $C_{ss}$  = plasma concentration in steady state, CT = citalopram, EM = extensive metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), IM = intermediate metaboliser (gene dose 0.5-1) (reduced CYP2D6 enzyme activity), In = natural logarithm, MR = metabolic ratio, NS = non-significant, OR = odds ratio, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant,  $t_{1/2}$  = half-life, UM = ultra-rapid metaboliser (gene dose 2) (increased CYP2D6 enzyme activity).

**Disclaimer**: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

## Brief summary and justification of choices:

Citalopram is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4. There is insufficient evidence to support a CYP2D6-(es)citalopram interaction (no/no-interactions).

None of the five studies investigating side effects found a significant effect of the CYP2D6 phenotype (Han 2013, Mrazek 2011, Peters 2008, Grasmader 2004 and Sindrup 1993). Of the four studies investigating efficacy, two large studies did not find an effect of the CYP2D6 phenotype (Mrazek 2011 (n = 1235) and Peters 2008 (n = 1953)). In addition, the two small studies contradicted each other. Han 2013 (n = 94) found a decrease in efficacy in patients with reduced CYP2D6 enzyme activity (intermediate metabolisers (IM)) and Tsai 2010 (n = 98) an increase. Both the small size of these studies and the contradictory result, suggest the results of these studies to be chance findings. Only four of the ten kinetic studies found a significant effect of reduced or absent CYP2D6 enzyme activity (intermediate or poor metaboliser (IM or PM)) on the plasma concentration or AUC of (es)citalo-pram (Chen 2013, de Vos 2011, Fudio 2010 and Herrlin 2003). The effect was small in all four of these studies; an increase by 20-24% for IM and a decrease of S-citalopram by 15% for PM.

You can find a detailed overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

Source	Code	Effect					Comments
ref. 1 - citalopram3Chen B et al.Estimation ofCYP2D6*10 geno-types on citalopramdisposition in Chine-se subjects by popu-lation pharmacoki-netic assay.J Clin Pharm Ther2013;38:504-11.PubMed PMID:23981149.	3	2C19 poor r 20 mg citald was exclude Genotyping - 4x *1/*1 (2 - 7x *1/*10 (	metaboliser opram on tw ed. :x CYP2C19 2x CYP2C2	selected for the phenotype, re to separate occ 9 *1/*1, 2x CYF 19 *1/*1, 5x CY 2C19 *1/*1, 7x	ceived a single casions. Co-m 2C19 *1/*2) ′P2C19 *1/*2)	e dose of edication	Authors' conclu- sion: 'CYP2C19 and CYP2D6 genotypes have impacts on the CL/F of citalo- pram.'
		Results: Results ve	rsus *1/*1: CYP2- C19 ge- notype all *1/*1	*10/*10 x 1.55 (NS) x 1.21 (NS)	*1/*10 x 1.33 (NS) x 1.15 (NS)	value for *1/*1 1175 1175	AUC citalopram versus *1/*1 (for patients with CYP- 2C19 *1/*1, which is the large majority in the Netherlands): IM: 121%

The table below follows the KNMP definitions for EM, PM, IM and UM. The definitions of EM, PM, IM and UM used in the table below may therefore differ from the definitions used by the authors in the article.

ref. 1, continuation		(ng.h/ml)	*1/*2	x 1.79 (NS) x 1.41 (NS)	1175	
		Cl <sub>or</sub> (L/h)		x 0.68 (S) x 0.74 (S)	17.5	
			*1/*1	x 0.83 (NS) x 0.85 (NS)	17.5	
			*1/*2	x 0.57 (NS) x 0.70 (NS)	17.6	
				1/*1 was only determined for	Clor for	
		all patien			<b>C</b> (1	
	IM: AA			odelling, only the combinatio		
			and CrP2	D6 genotypes was found to b f Clar	ea	
		Significal				
				s for *10. This is the most im inse population.	portant	
ref. 2 - escitalo-	3			depressive disorder were trea		Authors' conclu-
pram				day for 12 weeks. Patients wi		sion:
Han KM et al. CYP2D6 P34S				the 21-item Hamilton Depres		'Our results suggest that the P
polymorphism and				<ol> <li>were included. 56 patients atients withdrew because of a</li> </ol>		allele of the CYP-
outcomes of escita-				efficacy, personal conflict or c		2D6 P34S polymor-
lopram treatment in				to treatment, or adverse eve		phism is a favora-
Koreans with major		•		as a reduction of 50% or mo		ble factor in escita-
depression.		HAMD-21	score. Remi	ssion was defined as a HAM	D-21	lopram treatment
Psychiatry Investig 2013;10:286-93.			•	s. The side-effects profile wa		for MDD, and that the CYP2D6 P34S
PubMed PMID:				or Kliniske Undersogelser (U	KU) Side	polymorphism may
24302953.			ing Scale (UI			be a good genetic
				gs, such as antipsychotics a		marker for predic-
		were not.	were exclud	ed, but CYP2D6 inhibitors or	inducers	ting escitalopram
			aistic reares	sion analysis with sex and ag	le as	treatment outco-
				investigate the association of		mes.'
			nent efficacy			
		Genotypin				
		- 28x *1/*1				
		- 38x *1/*1				
		- 28x *10/*	<sup>•</sup> 10			
		Results:				
		Results f	or *10/*10 ve	ersus *1/*10 versus *1/*1:		
				OR (95% CI)	value	
					for	
		0/ 5			*1/*1	
		% of	1 week	NS	7.4%	
		pa- tients	2 weeks 4 weeks	NS trend for a decrease (p =	13% 36%	
		with	+ WCCK2	0.055 (NS)	50 /0	
		remis-		Also a trend for a decrea-		
		sion		se (p = 0.054) (NS) for		
				*10/*10 versus *1/*1+		
				*1/*10.		
			8 weeks	0.38 (0.15-0.98) (S)	32%	
				0.12 (0.01-0.90) (S) for		
				*10/*10 versus *1/*1+ *1/*10.		
	IM: C		12 weeks	0.36 (0.16-0.81) (S)	53%	
				0.12 (0.02-0.61) (S) for		
				*10/*10 versus *1/*1+		
				*1/*10.		
		% of	1 week	NS	11%	
		respon-	2 weeks	NS	33%	
		ders		Trend for a decrease (p = 0.099) (NS) for *10/*10		
1				versus *1/*1+*1/*10.		

ref. 2, continuation       4 weeks       trend for a decrease (p = 04%)         4 weeks       0.060 (NS)       NS for *10/*10 versus         NS for *10/*10 versus       74%         0.28 (0.99-0.80) (S) for       74%         12 weeks       0.21 (0.90-0.81) (S) for         10 week       weeks         10 weeks       0.10 (0.22-34) (S) for         10 weeks       NS         10 we	ref. 2, continuation			4 weeks		64%	
rof. 3 - escitalo- pran escital- prantice steady state escital- prantice steady state escitaloprantice (ENNEP)       3 194 patients were treated with escitaloprant 10-30 mg/dy. NOTE: Genotypes/Phenotypes: -14x PM -14x PM Elodod samples were collected 1-4 hours after taking the daily dose. A total of 7 patients used CYP2D6 inhibitors, but correction was performed for co-medication. Genotypes/Phenotypes: -14x PM -1x UM Blood samples were collected 1-4 hours after taking the daily dose. A total of 7 patients used CYP2D6 inhibitors, but correction was performed for co-medication. Gene dose 0.5 versus gene dose 2: - increased in(Ca* escitalopram) from 0.44 to 0.91 µg/L per mg (S) - Exercise in the ratio of escitalopram) gion - decrease in the ratio of escitalopram) gion - decrease in the ratio of escitalopram) gion - decrease in the ratio of escitalopram) gion - this corresponds to an increase in Ca* escitalopram by et (Mir AA - metabolic ratio (NS) NOTE: Genotyping for *3 through *11, *14A, *15, *17, *19, - 20, *20, *34, *41, *41 and gene duplication (*1, *2 and *35).       Authors' conclu- ston: - Significant asso- ciation of CYP2D6							
ref. 3 - escitalo- pram lindu- concentration in GENDEP 21926427.     3     Authors' conclu- side associated bit concentration in creased in (Cast escitalopram) from 0.44 to 0.91 µgL, per mol (S)     Authors' conclu- side associated with association bitween Gen otypes/phenotypes:       ref. 4 - citalopram de Vos A t al Association bitween CVP2C1617 and     3     Routine thrapping (S) consignificant differences in ln(Cast" escitalopram) (row as performed for co-medication.     Authors' conclu- sion: "Subject with an increase in Cast" escitalopram by 60% (rom 1.5 to 2.4 µgL) cert association for 3.4 µgL) cert association for 3.4 µgL cert association for a significant differences in ln(Cast" escitalopram by 60% (rom 1.5 to 2.4 µgL) cert association for a significant differences in ln(Cast" escitalopram by 60% (rom 1.5 to 2.4 µgL) cert association for a significant differences in ln(Cast" escitalopram by 60% (rom 1.5 to 2.4 µgL) cert association for a significant differences in ln(Cast" escitalopram by 60% (rom 1.5 to 2.4 µgL) certain association consentration in Genetopse (sherotypes)     Authors' conclu- sion: "Subject who had one associa- ted with por meta- bolizer phenotypes: - 14x PM       PM: AA UM: AA UM: AA Association bitween coversentiation in de Vos A t al Association bitween coversentiation in de Vos A t al Association bitween coversentiation in cert 4 - citalopram do Vos A t al Association bitween certain bit therapeutic drug monitoring was performed on 338 patents being treated with thatiopram.     Authors' conclu- sion: "Subject and association certain the transpectication in certain the case performed on 338 patents being treated with thatiopram.						-	
8 weeks         0.45 (0.22.0.39) (S)         74%           8 weeks         0.45 (0.22.0.39) (S) for *10/*10 versus *1/*1+ *1/*10.         74%           12 weeks         0.21 (0.08-0.54) (S)         88%           0.21 (0.08-0.54) (S)         88%           0.09 (0.02-0.34) (S) for *10/*10 versus *1/*1+ *1/*10.         88%           0.21 (0.08-0.54) (S)         88%           0.21 (S)         84%           104 patients were treated with escitalopram 10-30 mg/day.           9 (S)         94 patients were treated with escitalopram 10-30 mg/day.           9 (S)         94 patients were collected 1-4 hours after taking the daily dose A total of 7 patients used CVP2D6 inhibitors, but correction was peformed for co-medication.							
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ref. 4 - citalopram       3       Reference       12 weeks       0.21 (0.02-0.34) (S) for +10*10 versus *1/*1+ +11*10.       88%         ref. 4 - citalopram       3       Reference       NS       1         escita- lopram       psychic       NS       1       1         escita- lopram       side effects       NS       1       1         autonomic       NS       1       1       1       1         ref. 3 - escitalo- pram       NOTE: Cenotyping was for *10. This is the most important gene variant in this Korean population.       NS       1       1         Paychopharmacol 2012;26:398-007.       3       194 patients were treated with escitalopram 10-30 mg/day.       Authors' conclu- sion:       1         PubMed PMID: 21926427.       3       194 patients were collected 1-4 hours after taking the daily dose. A total of 7 patients used CYP2D6 inhibitors, but correction was performed for co-medication.       Social of MPM       1         21926427.       Cher gene dose 0.5 versus gene dose 2:       -       no secialopram to differences in In(Cs* escialopram) from 0.44 to 0.91 µg/L per mg (S)       -       -         -       into: Treased In(Cs** escialopram) from 0.44 to 0.91 µg/L per mg (S)       -       -       -       -         -       into: Those versus in Cs** escialopram) and the metabolic ratio 0 fescialopram/desmethylescitalo- ram osign							
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ref. 3 - escitalo- pram       3       194 patients were treated with escitalopram 10-30 mg/day. sexual       Authors' conclu- sion:       Authors' conclu- sion:         ref. 3 - escitalo- pram       3       194 patients were treated with escitalopram 10-30 mg/day. Ineadache       Authors' conclu- sion:       Authors' conclu- sion:         ref. 3 - escitalo- pram       3       194 patients were treated with escitalopram 10-30 mg/day. Ineadache       Authors' conclu- sion:       Authors' conclu- sion:         ref. 4 - citalopram de Vos A et al. Association between de Vos A et al. Association between de Vos A et al.       3       PM: AA UM: AA LM: AA LM: AA       PM: AA LM: AA LM: AA       Other gene doses 0: 5 versus gene dose 2: - increased In(Cs* escitalopram/tesmethylescitalo- pram by 34% (from 0.41 to 0.27) (S)       Authors' conclu- sion:         ref. 4 - citalopram de Vos A et al. Association between CYP2D6/171 r and       3       Routine therapeutic drug monitoring was performed on 338 patients being treated with citalopram. CYP2D6/171 r and       Authors' conclu- sion:					NS		
ref. 3 - escitalo- pram       3       194 patients were treated with escitalopram 10-30 mg/day. Isexual NS       Authors' conclusion: Sexual NS         ref. 3 - escitalo- pram       3       194 patients were treated with escitalopram 10-30 mg/day. Isexual NS       Authors' conclusion: Sexual NS         ref. 3 - escitalo- pram       3       194 patients were treated with escitalopram 10-30 mg/day. Isexue does 2: 28x gene dose 1.5)       Authors' conclusion: Subjects who had one CYP2D6 allele associated with allele)         2012:26:398-407. PubMed PMID: 21926427.       - 14x PM       Autors does 2: - 1x VM       Authors' conclusion: Subjects who had one concentration in Genotypes/phemotypes: - 7x UM         2012:26:398-407. PubMed PMID: 21926427.       - 61x CMC - 7x UM       Blood samples were collected 1-4 hours after taking the daily dose. A total of 7 patients used CYP2D6 inhibitors, but correction was performed for co-medication.       Gene dose 0.5 versus gene dose 2: - increased In(Css* escitalopram) from 0.44 to 0.91 µg/L per mg (S)       - decrease in the ratio of escitalopram/desmethylescitalo- pram by 34% (from 0.41 to 0.27) (S)       - decrease in the ratio of escitalopram/desmethylescitalo- pram by 34% (from 0.41 to 0.27) (S)         ref. 4 - citalopram de Vos A et al. Association between CYP2C19*17 and       3       Routine therapeutic drug monitoring was performed on 338 patients being treated with citalopram.       Authors' conclu- sion: "Significant asso- ciation of CYP226					NS		
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ref. 3 - escitalo- pram       3       194 patients were treated with escitalopram 10-30 mg/day. Ineadache       Authors' conclu- sion:         VP2C19 genotype predicts steady state escitalopram Concentration in GENDEP.       3       194 patients were treated with escitalopram 10-30 mg/day. Genotypes/phenotypes:       Authors' conclu- sion:         194 patients were treated with escitalopram 10-30 mg/day. predicts steady state escitalopram Concentration in GENDEP.       3       194 patients were treated with escitalopram 10-30 mg/day. - 91x EM (63x gene dose 2; 28x gene dose 1.5) - 82x EM (67x gene dose 1; 14x gene dose 0.5; 1x *17/null allele)       Authors' conclu- sion:         194 patients were treated with escitalopram concentration in GENDEP.       - 91x EM (63x gene dose 2; 28x gene dose 0.5; 1x *17/null allele)       Authors' conclu- sion:         194 patients were collected 1-4 hours after taking the daily dose. A total of 7 patients used CYP2D6 inhibitors, but correction was performed for co-medication.       Authors' conclu- boizer (i.e. IM/PM genotypic category) had a higher mean on concentra- tion than CYP2D6 extensive metabo- lizers (EMS).*         21926427.       PM: AA UM: AA UM: AA UM: AA UM: AA       Other gene doses versus gene dose 2: - no significant differences in ln(Csa* escitalopram) from 0.44 to 0.91 µg/L per mg (S)       Dither gene doses versus gene dose 2: - no significant differences in ln(Csa* escitalopram) and the metabolic ratio (NS)       Authors' conclu- sion than CYP2D6 extensive metabo- lizers (EMS).*         PM: AA UM: AA UM: AA Evos A et al. Association between CYP2C19'17 and       3       Routhors' conclu- sion of CYP2D6				•	NS		
skin       NS         hormonal       NS         hormonal       NS         sexual       NS         headache       NS         headaspan       Authors' conclusion			eneota		NS		
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sexual         NS           neadache         NS           neadache         NS           NOTE: Genotyping was for *10. This is the most important gene variant in this Korean population.         Authors' conclu- sion:           Pram         3         194 patients were treated with escitalopram 10-30 mg/day.           Genotypes/phenotypes:         - 91x EM (63x gene dose 2; 28x gene dose 1.5)         - 82x EM (67x gene dose 1; 14x gene dose 0.5; 1x *17/null allele)         - 82x EM (67x gene dose 1; 14x gene dose 0.5; 1x *17/null allele)         - 7x UM           Orgenzing Sentation in GENDEP.         - 14x PM         - 7x UM         - 7x UM         - 7x UM           21926427.         Blood samples were collected 1-4 hours after taking the daily dose. A total of 7 patients used CYP2D6 inhibitors, but correction was performed for co-medication.         - increased in(Csa* escitalopram from 0.44 to 0.91 µg/L per mg (S)         - this corresponds to an increase in Csa* escitalopram by 60% (from 0.41 to 0.27) (S)         - decrease in the ratio of escitalopram/desmethylescitalo- pram by 34% (from 0.41 to 0.27) (S)         - no significant differences in In(Csa* escitalopram) and the metabolic ratio (NS)         - NOTE: Genotyping for *3 through *11, *14A, *15, *17, *19, *20, *29, *36, *40, *41 and gene duplication (*1, *2 and *35).         - Nuthors' conclu- sion: "Significant asso- ciation of CYP226							
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IM: AA UM: AA- no significant differences in ln(Css <sup>a</sup> escitalopram) and the metabolic ratio (NS)NOTE: Genotyping for *3 through *11, *14A, *15, *17, *19, *20, *29, *36, *40, *41 and gene duplication (*1, *2 and *35).ref. 4 - citalopram de Vos A et al. Association between CYP2C19*17 and3Routine therapeutic drug monitoring was performed on 338 patients being treated with citalopram. Genotypes:Authors' conclu- sion: "Significant asso- ciation of CYP2D6		PM: AA	Other gen	e doses vers	us dene dose 2 <sup>.</sup>		
UM: AAmetabolic ratio (NS)NOTE: Genotyping for *3 through *11, *14A, *15, *17, *19, *20, *29, *36, *40, *41 and gene duplication (*1, *2 and *35).ref. 4 - citalopram de Vos A et al. Association between CYP2C19*17 and3Routine therapeutic drug monitoring was performed on 338 patients being treated with citalopram. Genotypes:Authors' conclu- sion: "Significant asso- ciation of CYP2D6						) and the	
*20, *29, *36, *40, *41 and gene duplication (*1, *2 and *35).ref. 4 - citalopram de Vos A et al. Association between CYP2C19*17 and3Routine therapeutic drug monitoring was performed on 338 patients being treated with citalopram.Authors' conclu- sion: "Significant asso- ciation of CYP2D6		UM: AA	-			,	
*20, *29, *36, *40, *41 and gene duplication (*1, *2 and *35).ref. 4 - citalopram de Vos A et al. Association between CYP2C19*17 and3Routine therapeutic drug monitoring was performed on 338 patients being treated with citalopram.Authors' conclu- sion: "Significant asso- ciation of CYP2D6			NO		<b></b>		
ref. 4 - citalopram de Vos A et al.3Routine therapeutic drug monitoring was performed on 338 patients being treated with citalopram.Authors' conclu- sion: "Significant asso- ciation of CYP2D6CYP2C19*17 and3Genotypes/phenotypes:authors' conclu- sion: "Significant asso- ciation of CYP2D6							
de Vos A et al.patients being treated with citalopram.sion:Association between CYP2C19*17 andGenotypes/phenotypes:"Significant asso- ciation of CYP2D6	ref. 4 - citalopram	3					Authors' conclu-
Association between CYP2C19*17 and"Significant asso- ciation of CYP2D6		-		•	<b>a i</b>	2000	
	Association between		•	C			
metabolism of    - 170x EM (*1/*1)   genotype with cita-					:		
					١		
amitriptyline, citalo- pram and clomipra 127x IM (gene dose 1) - 34x PM (gene dose 0)Iopram metabolism was observed."							•
mine in Dutch hospi- $-7x UM (gene dose \ge 3)$							1000 UDOCI VOU.
	talized patients.			,	- /		

P			<u>.                                    </u>
Pharmacogenomics J 2011;11:359-67.		The citalopram dose was known for 223 patients (111x EM, 81x IM, 26x PM, 5x UM). Relevant co-medication was not excluded.	
PubMed PMID: 20531370.		IM versus EM:	
ref. 4, continuation	IM: A	<ul> <li>increase in the dose by 14% (from 28 to 32 mg/day) (S)</li> <li>increase in the dose-corrected C<sub>ss</sub> citalopram by 20% (from 2.5 to 3.0 μg/L per mg/day) (S)</li> <li>increase in the ratio of citalopram/desmethylcitalopram by 19% (from 2.6 to 3.1) (S)</li> </ul>	
	PM: AA	<ul> <li>PM versus EM:</li> <li>no difference in dose (both 28 mg/day) (NS)</li> <li>increase in the dose-corrected C<sub>ss</sub> citalopram by 16% (from 2.5 to 2.9 μg/L per mg/day) (NS)</li> <li>decrease in the ratio of citalopram/desmethylcitalopram by 7.7% (from 2.6 to 2.4) (NS)</li> </ul>	Plasma concen- tration versus EM: IM: 120% PM: 116% UM: 84%
	UM: AA	<ul> <li>UM versus EM:</li> <li>no significant difference in dose (24 versus 28 mg/day) (NS)</li> <li>decrease in the dose-corrected C<sub>ss</sub> citalopram by 16% (from 2.5 to 2.1 μg/L per mg/day) (NS)</li> <li>decrease in the ratio of citalopram/desmethylcitalopram by 12% (from 2.6 to 2.3) (NS)</li> </ul>	
		NOTE: Genotyping for *3 through *6 and gene duplica-tion.	
<b>ref. 5 - citalopram</b> Mrazek DA et al. CYP2C19 variation and citalopram response.	3	1235 white patients without Latin-American, Portuguese or Spanish ancestry were treated with citalopram 20-60 mg/day. Genotypes/phenotypes:	Authors' conclu- sion: "No relationship between CYP2D6 genotype-based
Pharmacogenet Genomics 2011;21:1-9. PubMed PMID: 21192344.		- 36% EM (gene doses 2 and 2.5) - 44% gene doses 1 or 1.5 - 13% PM or gene dose 0.5 - 6% UM (gene dose ≥ 3)	categories and either remission or tolerance was identified."
		A total of 1074 patients used citalopram for at least 6 weeks. Co-medication with an effect on CYP2D6 was not excluded.	
	IM: AA PM: AA	CYP2D6 genotypes: - were non-significantly associated with tolerance (NS). Intolerance was defined as leaving the study, or not conti- nuing with citalopram at the end of the study due to adver- se events. - were non-significantly associated with remission (NS).	
	UM: AA	Remission was defined as a score ≤ 5 on the 16-item Quick Inventory of Depressive Symptomatology – Clinical Rating.	
	-	NOTE: Genotyping for *2A, *2 through *12, *14, *17, *41 and gene duplication. NOTE: The assignment of gene dose 0.5 to *2 and gene dose 1.5 to *2A differs from our system (gene dose 1 for *2).	
<b>ref. 6 - escitalo-</b> pram Tsai MH et al.	3	A total of 98 patients were treated with escitalopram (4 weeks 10 mg/day, followed by 4 weeks 10-30 mg/day).	Authors' conclu- sion: "The group of
Genetic polymor- phisms of cytochro- me P450 enzymes		Genotypes/phenotypes: - 57x EM (16x gene dose 2; 41x gene dose 1.5) - 41x IM (12x gene dose 0.5; 29x gene dose 1 (of which 26x	patients with gene dose 0.5 had a significantly higher
influence metabo- lism of the antide- pressant escitalo-		*10/*10)) Co-medication with an effect on CYP2D6 was not excluded.	frequency of remit- ters from major depressive disorder

2010;11:537-46.       HAA-D (mean 22.14).       HAA-D (mean 22.14).         20350136.       IM:AA       -no difference in dose and C <sub>80</sub> of escitalopram and metabolitos       DCIT or the S.         2010;21:537-46.       -no difference in C <sub>80</sub> of escitalopram and desmethylescita- lopram between gree dose 0.5 and gene doses 1 through 2       DCIT or the S.         2010;21:22.       - no difference in C <sub>80</sub> of escitalopram and desmethylescita- lopram between gree dose 0.5 and gene doses 1 through 2       DCIT or the S.         2.       - no difference in C <sub>80</sub> of escitalopram and desmethylescita- lopram between gree dose 0.5 and gene doses 1 through 2       DCIT or the S.         2.       - no difference in C <sub>80</sub> of escitalopram and desmethylescita- lopram between gree dose 0.5 and gene dose of 200% citalopram.       DCIT or the S.         ref. 7 - citalopram       These are the most common polymorphisms in this (ethni- cally Chinese) population.       Nother second the state and the				
ref. 7 - citalopram Fuldi S et al.         cally Chinese) population.         Authors' conclu- sion:           Evaluation of the influence of sex and CYP2C19 and CYP- 2016 polymorphisms in the disposition of citalopram.         a cross-over study, 35 healthy volunteers (27x EM, 8x IM).         Authors' conclu- sion:         "CYP2D6 volun- trees/eval a single dose of 20 mg citalopram. The formulation of citalopram varied between the two parts of the study, CYP2C19 and CYP- 2016,c266:200-4.         "CYP2D6 volun- medication, smokers and alcohol consumption were exclu- ded.         "CYP2D6 volun- medication, smokers and alcohol consumption were exclu- ded.         "CYP2D6 volun- macokinetic model.           1M versus EM: - increase in the predicted AUC <sup>b</sup> by 23.7% (from 3112.7 to 3351.6 ng,hour/mL per ng/kg) (S)         - - decrease in the predicted AUC <sup>b</sup> by 16.1% (from 6.27 to 5.26 mL/min per kg) (S)         in association with CYP2C19 *1/*1 while its influence is association with CYP2C19 *1/*1           19840783.         IM versus EM for volunteers who are CYP2C19 *1/*1 (n=26): - no significant increase in the predicted AUC <sup>b</sup> by approx. 60% (from approx. 2500 to approx. 4000 ng,hour/mL per mg/kg) (S)         NUC Citalopram versus EM: IN: 124%           ref. 8 - citalopram Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to cot cloarpram in the STAR*D sample. PLoS One 20063:ref172.         3 The same study as in Mraze KD et al., 2009, but here analysis of the data was performed for all Caucasian and African-American patients. A total of 1953 patients, who were treated with citalopram 20-60 mg/day, were divided over two case-contol studies or tolerance to cot clatopram patients. PubMed PMID: 183822661.         Authors' conclu- sin both	response. Pharmacogenomics 2010;11:537-46. PubMed PMID: 20350136.	IM: AA	<ul> <li>Hamilton Depression Scale (HAM-D; maximum score of 21 points). Upon inclusion, the patients had a score ≥ 14 on the HAM-D (mean 22.14).</li> <li>no difference in dose and C<sub>ss</sub> of escitalopram and metabolites between the various allele combinations</li> <li>no difference in C<sub>ss</sub> of escitalopram and desmethylescitalopram between gene dose 0.5 and gene doses 1 through 2</li> <li>higher percentage of patients with remission for gene dose 0.5 compared to gene doses 1 through 2 (100% versus approx. 70%) (S)</li> <li>NOTE: Genotyping for *4, *5, *10 and gene duplication.</li> </ul>	treatment. Howe- ver, serum concen- trations of S-CIT, S- DCIT or the S- DCIT:S-CIT ratio in the patients at 0.5 gene dose of CYP2D6 were not shown to be signi- ficantly higher than the non-0.5 gene dose groups over the 8-week treat-
ref. 7 - citalopram       3       In a cross-over study, 35 healthy volunteers (27 E LR & IM)       Authors' conclusion:         Fudio S et al.       S       In a cross-over study, 35 healthy volunteers (27 E LR & IM)       Authors' conclusion:         CYP2C19 and CYP-       CYP2C19 and CYP-       CYP2C19 and CYP-       CYP2C19 and CYP-         2D6 polymorphisms       Raw data are not provided, only data predicted using a pharacitalopram.       Here are not provided, only data predicted using a pharacitalopram.         Eur J Pharmacol       IM: A       Nerses EM:       Nerses EM:       Nerses EM:         2010;525:200-4.       IM: Versus EM:       - increase in the predicted AUC <sup>b</sup> by 23.7% (from 3112.7 to 3851.6 ng, hour/mL per mg/kg) (S)       Set 16 ng, hour/mL per mg/kg) (S)       Set 16 ng, hour/mL per mg/kg) (S)         9840783.       IM versus EM for volunteers who are CYP2C19 *1/*1 (n=26):       - no significant increase in the predicted AUC <sup>b</sup> by approx. 60% (from a pprox. 2500 to approx. 4000 ng, hour/mL per mg/kg) (S)       AUC citalopram versus EM:         IM versus EM for volunteers who are CYP2C19 *1/*2 is greater for IM than for EM (37.5% versus 14.8%). Therefore, in this study, it appears that the genotypes are not independent.       NOTE: The percentage CYP2C19 *1/*2 is greater for IM than for EM (37.5% versus 14.8%). Therefore, in this study, it appears that the genotypes are not independent.       Note: secontrol studies of massociated vith out prepharmacokinetic genes control studies of me divide over two case-control studies of manalysis of the data was performed for all				
19840783.       - decrease in the predicted Cla <sup>in</sup> by 16.1% (from 6.27 to 5.26 mL/min per kg) (S)       in association with CYP2C19 *1/*1 (m=26): in o significant increase in the predicted AUC <sup>b</sup> (NS)         IM versus EM for volunteers who are CYP2C19 *1/*2 (n=7): - increase in the predicted AUC <sup>b</sup> by approx. 60% (from approx. 2500 to approx. 4000 ng.hour/mL per mg/kg) (S)       AUC citalopram versus EM: IM versus EM for volunteers who are CYP2C19 *1/*2 is greater for IM than for EM (37.5% versus 14.8%). Therefore, in this study, it appears that the genotypes are not independent. NOTE: The percentage CYP2C19 *1/*2 is greater for IM than for EM (37.5% versus 14.8%). Therefore, in this study, it appears that the genotypes are not independent. NOTE: The percentage CYP2C19 *1/*2 is greater for IM than for EM (37.5% versus 14.8%). Therefore, in this study, it appears that the genotypes are not independent. NOTE: Genotyping was only performed for all Caucasian and African-American patients. A total of 1953 patients, who were treated with citalopram influence response or tolerance to citalopram in the STAR*D sample. PLoS One 2008;3re1872. PubMed PMID: 18382661.       Authors' conclu- sion: "No genetic poly- morphism in the study lasted 12 weeks. Only patients who used citalo- pram for more than 6 weeks were used in analysis of response parameters. Caucasian and African-American patients were analysed separately.       Authors' conclu- sion: "No genetic poly- morphism in the patients were analysed separately.         CYP2D6 gene doses: - were non-significantly associated with tolerance (NS). Intolerance was defined as leaving the study, or not conti- nuing with citalopram at the end of the study due to adver- se events. - were non-significantly associated with response (NS).       Not At were non-significantly associated with response (NS).	Fudio S et al. Evaluation of the influence of sex and CYP2C19 and CYP- 2D6 polymorphisms in the disposition of citalopram. Eur J Pharmacol	3	In a cross-over study, 35 healthy volunteers (27x EM, 8x IM) received a single dose of 20 mg citalopram. The formulation of citalopram varied between the two parts of the study. Co- medication, smokers and alcohol consumption were exclu- ded. Raw data are not provided, only data predicted using a phar- macokinetic model. IM versus EM:	sion: "CYP2D6 volun- teers carrying *1/*4 have an AUC 23% higher than wild type. Our data also suggest that the influence of CYP-
ref. 8 - citalopram Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS One 2008;3:e1872. PubMed PMID: 18382661.3The same study as in Mrazek DA et al., 2009, but here analysis of the data was performed for all Caucasian and African-American patients. A total of 1953 patients, who were treated with citalopram influence response or tolerance to citalopram in the STAR*D sample. PLoS One 2008;3:e1872. PubMed PMID: 18382661.3Authors' conclu- sin: "No genetic poly- morphism in the pharmacokinetic genes examined was significantly associated with tolerance (NS). Intolerance was defined as leaving the study, or not conti- nuing with citalopram at the end of the study due to adver- se events. - were non-significantly associated with response (NS).Authors' conclu- sion: "No genetic poly- morphism in the pharmacokinetic genes examined was significantly associated with tolerance (NS).IM: AAIM: AA		IM: A	<ul> <li>decrease in the predicted Clor<sup>a</sup> by 16.1% (from 6.27 to 5.26 mL/min per kg) (S)</li> <li>IM versus EM for volunteers who are CYP2C19 *1/*1 (n=26):</li> <li>no significant increase in the predicted AUC<sup>b</sup> (NS)</li> <li>IM versus EM for volunteers who are CYP2C19 *1/*2 (n=7):</li> <li>increase in the predicted AUC<sup>b</sup> by approx. 60% (from approx. 2500 to approx. 4000 ng.hour/mL per mg/kg) (S)</li> <li>NOTE: The percentage CYP2C19 *1/*2 is greater for IM than for EM (37.5% versus 14.8%). Therefore, in this study, it appears that the genotypes are not independent.</li> </ul>	in association with CYP2C19 *1/*1 while its influence is more apparent in association with CYP2C19*1/*2." AUC citalopram versus EM:
PM: AA Response was defined as a reduction in the score on the 16-item Quick Inventory of Depressive Symptomatology	Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS One 2008;3:e1872. PubMed PMID:		The same study as in Mrazek DA et al., 2009, but here analysis of the data was performed for all Caucasian and African-American patients. A total of 1953 patients, who were treated with citalopram 20-60 mg/day, were divided over two case-control studies (research study (n=831) and validation study (n=1046)). Co-medication with an effect on CYP2D6 was not excluded. The study lasted 12 weeks. Only patients who used citalo- pram for more than 6 weeks were used in analysis of response parameters. Caucasian and African-American patients were analysed separately. CYP2D6 gene doses: - were non-significantly associated with tolerance (NS). Intolerance was defined as leaving the study, or not conti- nuing with citalopram at the end of the study due to adver- se events. - were non-significantly associated with response (NS). Response was defined as a reduction in the score on the	sion: "No genetic poly- morphism in the pharmacokinetic genes examined was significantly associated with our response or tole- rance phenotypes

ref. 8, continuation		<ul> <li>were non-significantly associated with remission (NS).</li> <li>Remission was defined as a score ≤ 5 on the QIDS-SR.</li> <li>PM versus (EM+IM+UM):</li> </ul>	
		- no significant difference in tolerance and response (NS)	
		- no significant decrease in the dose (NS)	
		<ul> <li>no significant difference in the duration of use of citalopram (NS)</li> </ul>	
	0	NOTE: Genotyping for *3 through *9.	
ref. 9 - citalopram Grasmader K et al. Impact of polymor- phisms of cytochro- me-P450 isoenzy- mes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical	3 PM: AA	Genotyping was performed on 136 patients on antidepressants, including 15 patients on citalopram (dose unknown). Out of the 15 patients on CT, 2 were CYP2D6 PM, the other 13 patients were either CYP2D6 IM or EM. Co-medication was permitted. The median dose-corrected $C_{ss}$ was 1.60 ng/mL per mg of dosed CT. For the two PMs, the corrected plasma concentration was 70% and 39% higher than the median. Both experienced relevant side effects.	Plasma concentra- tion versus EM + IM: PM: 155%
setting. Eur J Clin Pharma- col 2004;60:329-36.			
ref. 10 - citalopram	3	12 healthy volunteers (6x EM, 6x PM; all CYP2C19 EM)	
Herrlin K et al. Metabolism of cita- lopram enantiomers		received citalopram 20 mg/day for 7 days, no relevant co- medication;	
in CYP2C19/CYP- 2D6 phenotyped panels of healthy		<ul> <li>PM versus EM:</li> <li>decrease in AUC of racemic mixture from 1398 to 1392 nM/h (by 0.4%, significance unknown)</li> </ul>	AUC citalopram versus EM: PM: 100%
Swedes. Br J Clin Pharmacol 2003;56:415-21.	PM: A	<ul> <li>decrease in AUC S-CT from 530 to 451 nM/h (S by 15%).</li> <li>no significant difference for AUC R-CT.</li> <li>increase in AUC S-desmethyl-CT from 208 to 237 nM/h (NS by 14%) and for R-desmethyl-CT from 233 to 251 nM/h (NS by 8%).</li> <li>decrease in AUC didesmethyl-CT from 96 nM/h to below the quantification limit (S by 100%)</li> </ul>	AUC S-citalopram versus EM: PM: 85%
		NOTE: Genotype unknown.	
<b>ref. 11 - citalopram</b> Carlsson B et al. Enantioselective analysis of citalo-	4	19 adolescents (14x EM, 3x IM, 2x UM) were treated with citalopram 10-60 mg/day. Co-medication other than oral contraception is rare. A total of 53% were smokers.	
pram and metabo- lites in adolescents. Ther Drug Monit 2001;23:658-64.	IM: AA	<ul> <li>IM versus EM:</li> <li>decrease in C<sub>ss</sub><sup>a</sup> racemic mixture from 5.97 to 4.82 nmol/L per mg (significance unknown, by 19%)</li> <li>decrease in C<sub>ss</sub><sup>a</sup> S-CT from 2.21 to 1.65 nmol/L per mg (significance unknown, by 26%)</li> <li>decrease in C<sub>ss</sub><sup>a</sup> R-CT from 3.76 to 3.17 nmol/L per mg (significance unknown, by 16%)</li> </ul>	C <sub>ss</sub> ª citalopram versus EM: IM: 81% UM: 43%
	UM: AA	<ul> <li>UM versus EM:</li> <li>decrease in C<sub>ss</sub><sup>a</sup> racemic mixture from 5.97 to 2.58 nmol/L per mg (significance unknown, by 57%)</li> <li>decrease in C<sub>ss</sub><sup>a</sup> S-CT from 2.21 to 0.94 nmol/L per mg (significance unknown, by 58%)</li> <li>decrease in C<sub>ss</sub><sup>a</sup> R-CT from 3.76 to 1.54 nmol/L per mg (significance unknown, by 59%)</li> </ul>	C <sub>ss</sub> ª S-citalopram versus EM: IM: 74% UM: 42%

rof 11 continue		NOTE: Constructing was performed for the alleles *2 *4 and	
ref. 11, continua-		NOTE: Genotyping was performed for the alleles *3, *4 and	
tion	2	*6 and for gene duplication.	
<b>ref. 12 - citalopram</b> Bondolfi G et al. Non-response to citalopram in depressive patients: pharmacokinetic and clinical conse- quences of a fluvo- xamine augmenta- tion. Psychopharmacolo- gy	3 PM: AA	<ul> <li>7 female patients (6x EM, 1x PM; all CYP2C19 EM) were first treated with citalopram 40 mg/day for 3 weeks, followed by the addition of fluvoxamine 50 mg/day for 3 weeks. Benzodiazepines, chloralhydrate and non-relevant co-medication were permitted.</li> <li>PM: <ul> <li>Css citalopram and desmethylcitalopram were within the range observed for the other patients.</li> </ul> </li> <li>NOTE: Genotype unknown.</li> </ul>	
1996;128:421-5.			
<b>ref. 13 - citalopram</b> Sindrup SH et al. Pharmacokinetics of citalopram in rela- tion to the sparteine and the mepheny- toin oxidation poly- morphisms. Ther Drug Monit 1993;15:11-7.	3 PM: A	<ul> <li>24 healthy volunteers received citalopram 40 mg/day for 10 days. The data of 18 volunteers (10x EM, 8x PM; all CYP-2C19 EM) were presented.</li> <li>PM versus EM: <ul> <li>increase in AUC citalopram from median 4588 to 4700 nM.hour (NS, by 2%)</li> <li>increase in t<sub>1/2</sub> from median 30 to 36 hours (NS, by 20%)</li> <li>increase in AUC desmethylcitalopram from median 1768 to 2400 nM.hour (S, by 36%)</li> <li>decrease in AUC didesmethylcitalopram from median 370 nM.hour to undetectable (S, by 100%)</li> <li>no difference in type or frequency of adverse events Citalopram is a weak inhibitor of CYP2D6.</li> </ul> </li> </ul>	AUC citalopram versus EM: PM: 98%
ref. 14 - escitalo-	0	No significant difference in exposure was observed in poor	
<b>pram</b> SPC Lexapro (esci- talopram) 05-09-13.	PM: AA	CYP2D6 metabolisers.	
ref. 15 - citalopram	0	In vivo research has demonstrated that the metabolites of	
SPC Cipramil (cita- lopram) 01-04-17.	PM: AA IM: AA UM: AA	citalopram do not exhibit any clinically relevant polymor- phisms of sparteine/debrisoquine oxidation (CYP2D6).	
ref. 16 - escitalo- pram SPC Lexapro (esci- talopram), USA, 04- 01-17.	0 PM: AA	Steady state levels of racemic citalopram were not signifi- cantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalo- pram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism.	
<b>ref. 17 - citalopram</b> SPC Celexa (citalo- pram), USA, 04-01- 17.	0 PM: AA	Citalopram steady-state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP- 2D6.	

 <sup>a</sup> Corrected for dose.
 <sup>b</sup> Corrected for dose and weight.
 NOTE: Phenotyping usually does not distinguish between IM, EM and UM. Therefore, EM in these studies is usually equal to IM+EM+UM.

Risk group	-
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## Comments:

Escitalopram is the S-enantiomer of citalopram, which is primarily responsible for the antidepressant and anxiolytic effect.

Date of literature search: 11 April 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmacogenetics	PM	4 A	No	No	14 May 2018
Working Group decision	IM	4 C	No	No	
	UM	4 AA	No	No	

## Mechanism:

Citalopram is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4 to N-desmethylcitalopram. N-desmethylcitalopram is converted to didesmethylcitalopram by CYP2D6.

Although desmethylcitalopram has antidepressant activity, the activity is low and clinically non-significant at standard doses (Herrlin, 2003).